Impact of recurrent Clostridium difficile infection: hospitalization and patient quality of life

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Running title: Impact of recurrent Clostridium difficile infection

Abstract

Objectives

Data quantifying outcomes of recurrent *Clostridium difficile* infection (rCDI) are lacking. We sought to determine the UK hospital resource use and health-related quality of life (HrQoL) associated with rCDI hospitalisations.

Patients and methods

A non-interventional study in 6 UK acute hospitals collected retrospective clinical and resource use data from medical records of 64 adults hospitalised for rCDI and 64 matched inpatient controls with a first episode only (f)CDI. Patients were observed from the index event (date rCDI/fCDI confirmed) for 28-days (or death, if sooner); UK-specific reference costs were applied. HrQoL was assessed prospectively in a separate cohort of 30 patients hospitalised with CDI, who completed the EQ-5D-3L questionnaire during their illness.

Results

The median total management cost (post-index) was £7,539 and £6,294 for rCDI and fCDI, respectively (cost difference, p=0.075); median length of stay (LOS) was 21 days and 15.5 days, respectively (p=0.269). The median cost difference between matched rCDI and fCDI cases was £689 (IQR=£-1,873-£3,954). Subgroup analysis demonstrated the highest median costs (£8,542/patient) in severe rCDI cases. CDI management costs were driven primarily by hospital LOS, which accounted for >85% of costs in both groups. Mean EQ-5D index values were 46% lower in CDI patients compared with UK population values (0.42 and 0.78, respectively); EQ-VAS scores were 38% lower (47.82 and 77.3, respectively).

Conclusions

CDI has considerable impact on patients and healthcare resources. This multicentre study provides a contemporaneous estimate of the real-world UK costs associated with rCDI management, which are substantial and comparable to fCDI costs.

Introduction

Clostridium difficile infection (CDI) is a major public health challenge worldwide, and is associated with significant morbidity, mortality and healthcare resource utilisation.[1–5] In the UK, although CDI reports decreased by 61% between 2007/08 and 2010/11 following the introduction of national surveillance, there was a 6% increase in CDI cases in England (from 24.8-26.3/100,000 population) between 2013/14 and 2014/15.[6–8]

A recent study undertaken in 2012-13 across 482 hospitals in 20 European countries reported a CDI incidence of 7 cases/10,000 patient-bed days, a 70% increase on rates recorded in 2008. Furthermore, when diarrhoeal samples were re-tested by an optimised method for diagnosing CDI, about a quarter of cases had been missed locally; consequently, the true rate of CDI in Europe is probably much higher.[9] In the US, *C. difficile* was recently reported to be the most common cause of healthcare associated infection, with approximately half-a-million CDI cases and 29,000 deaths in 2011.[10]

It is estimated that recurrent CDI (rCDI) following initial resolution occurs in 20-30% of patients.[11–13] However, data on the burden and outcomes associated with rCDI are scarce. Surveillance systems may fail to capture many rCDI cases given that re-testing of patients with symptoms suggestive of rCDI may not occur. Notably, mandatory surveillance data in England largely exclude rCDI cases, as the collected figures exclude repeat laboratory-positive results within 28-days from the same patient.[8] There is a lack of contemporaneous information quantifying the economic burden of CDI in the UK, and particularly the resource use associated with recurrent episodes. Such costs have growing relevance as new therapeutic options become available that reduce rCDI rates compared with conventional treatments.[14,15]

In addition to the economic burden, it is important to consider the impact of new CDI therapeutics on health-related quality of life (HRQoL); this may be impaired in CDI patients due to decreased functional capacity and anxiety about physical symptoms or complications.[16,17] Despite the high incidence of CDI,

its impact on HRQoL has not been widely studied and therefore conventional economic analyses may underestimate the true burden.

This industry-initiated study aimed to quantify the cost of hospital resource use (HRU) for patients with rCDI and describe the impact of CDI on HRQoL. The study was initiated by Merck Sharp and Dohme Limited (MSD) prior to the Phase 3 study for bezlotoxumab, which has subsequently been approved for prevention of CDI recurrence and was designed to provide "real-world" data that can be used to help determine the cost-effectiveness of new CDI management options.

Methods

A mixed-methodology non-interventional study was conducted between September-2013 and September-2014 in six geographically-dispersed UK National Health Service hospitals. Potential hospital sites likely to provide sufficient study participants and representation across NHS England regions and Scotland were identified by the lead investigator, study sponsor, and by review of Health Protection Agency (now PHE) mandatory surveillance data. Potential hospitals were approached and subsequently recruited to the study on the basis of their ability/capacity to deliver the study data collection requirements (including database systems that would allow identification of eligible patients; availability of local clinical staff to seek informed consent and collect the required data; and confirmed participant availability). Financial support for individual centres was provided in line with the National Institute for Health Research (NIHR) costing template, as is standard for studies implemented in the UK. Ethics committee (London-Brent, reference 13/LO/1046) and relevant local approvals were obtained. The study was undertaken in two parts:

Part 1: Matched retrospective cohort study

Design

A matched retrospective cohort study covering an observation period of 01-March-2012 to 02-June-2014 gathered clinical and HRU data from the medical records of patients hospitalised for rCDI and matched patients from the same centres, with a first episode of CDI but no recurrence (fCDI). The design and flow is summarised in **Figure 1**.

Patients

rCDI cases were adult (≥18 years) inpatients with a positive CD toxin test after 01-May-2012 (the index result) and any previous positive CD toxin test in the ≤12-weeks before this result. Potential patients were identified from microbiology records and eligibility confirmed by cross-referencing with hospital administration systems and full CDI testing records. Patients were included in the final dataset only where a matched (fCDI) control was identified (see below). May-2012 was chosen as the start of the observation period because the UK Department of Health issued revised guidance on *C. difficile* diagnosis and reporting in March-2012; hence, it was considered that there would be greater uniformity between centres in CDI testing after this date.[18] It was expected (although not confirmed) that included CDI cases would have been diagnosed according to this guidance; although all patients identified as eligible by the participating centres were included.

Matched fCDI controls were patients with a first CDI episode (community or healthcare-facility acquired) but no subsequent positive CD toxin test within the 12-weeks following last CDI treatment, who matched a rCDI case according to date of first positive CD toxin test (±12-weeks), age group (<75/≥75 years) and gender.

Patients were excluded if they transferred hospital trusts or died before the end of CDI treatment. All eligible paired patients were included. Patient consent was not required since this part of the study involved only routinely-collected clinical data gathered in pseudo-anonymised form by members of the direct care team.

Data collection

Pseudo-anonymised data were collected retrospectively by local clinical staff from eligible patients' hospital medical records using a standard data collection form. The dataset comprised baseline demographics; co-morbidities; CDI strain and illness severity at first episode (both groups) and recurrence (rCDI only); and HRU (hospital admission and discharge dates, length of stay [LOS] per ward/side room, outpatient appointments, Emergency Department [ED] attendances, prescribing, diagnostic tests, supplementary nutrition). HRU data were collected for the 'post-index' period, defined as the period between the index event (date rCDI or fCDI first confirmed by positive CD toxin test) and 28-days post-index or death, whichever was shorter. A 28-day observation period was chosen to reduce the risk of the results being skewed by non-CDI-related resource. Due to the acute nature of the disease, HRU occurring after 28-days was considered much less likely to be attributable to CDI. For rCDI, data were also collected for the 'between-episode' period (from 72-hours after end of treatment for the first CDI episode until the index event).

Resource costs were calculated using UK-specific reference costs (Supplementary appendix 1) and a Market Forces Factor Index applied to the costs for each Trust.[19–30]

Outcomes

The primary outcome was the difference in total hospital management costs between patients with rCDI and fCDI. Secondary outcomes included the difference in the number of days hospitalised during the post-index period and total management costs for the between-episode period (rCDI only).

Statistical analysis

We aimed to include 75 rCDI and 75 fCDI patients in the study. As there are no UK estimates of rCDI costs, the sample size was based on US data, which showed an average LOS for rCDI of 9-days and a cost range of $3,500-$5,000/recurrence (1999 Dollars).[31] Assuming similar UK costs and using the mid-point of this estimate converted to UK pounds (£2,800), a sample of 75 patients provided a 95% CI of £2,623-£2,977 (±£177 [6%]); this was considered to be interpretable to clinicians and payers given the magnitude of the cost difference between established and more expensive new therapeutics. Six

study centres were used, with the expectation of achieving the recommended sample size based on expected numbers of eligible paired patients.

Analysis was conducted using Microsoft Excel on the available data, with no imputation of missing values apart from a set of pre-specified assumptions (Supplementary Appendix 1). The number of patients available for each analysis is stated where data were missing. Descriptive endpoints are presented using the mean (standard deviation, SD), median (IQR) or percentages, as appropriate. The difference between rCDI and fCDI patients in the median total cost of treating CDI and the median LOS during the post-index period was compared using the Wilcoxon rank-sum test.

HRU endpoints are presented overall and stratified by CDI severity (a planned subgroup analysis). Severe CDI was defined by the presence of any of the following criteria: white cell count >15x10^9/L, acutely rising blood creatinine (e.g. >50% increase above baseline), temperature >38.5^{o}C or evidence of severe colitis (abdominal signs, radiology).[32] When none of these was present, CDI was classified as mild/moderate.

Part 2: Prospective patient self-assessment of QoL

Design

As HRQoL is not routinely measured and documented in medical records, it was assessed prospectively in a separate cohort of adult patients from the same centres, who were hospitalised with CDI. Eligible patients completed the EQ-5D-3L questionnaire[33,34] during their illness, within five-days of symptom onset. Questionnaires were completed between 10-September-2013 and 07-August-2014.

Demographic and disease history data including gender, age and CDI severity were recorded from the patients' medical records.

Patients

Patients were included if they had a positive CDI test, were hospital inpatients and aged ≥18 years at the date of the positive CDI test and consented to complete the questionnaire. Owing to the lack of data on HRQoL in CDI patients in general, part 2 was not restricted to rCDI and all patients with CDI (both first and recurrent episodes) were eligible for inclusion. Potentially eligible patients were identified from microbiology records and, if considered by clinical staff to be competent to consent, they were approached by a member of their care team with study information and asked if they wished to participate. Only consenting patients were included. Consecutive eligible patients were invited until the recruitment target was met (30 patients, maximum 10 patients/centre). A sample size of 30 patients was recommended, based on the Central Limit Theorem, assuming the results would be normally distributed.

Outcomes

The main outcomes were the mean (SD) EQ-5D index and visual analogue scale (VAS) scores.

Statistical analysis

The EQ-5D descriptive system was scored according to the published instructions.[35] EQ-5D index and VAS scores in patients with CDI were compared with published norms for the UK general population using Welch's t-test.[36] The EQ-5D population norm for patients aged 65-74 years was used for comparison, since the median age of patients in our study (70-years) was within this range.

Results

Part 1: Matched retrospective cohort study

<u>Demographics and CDI characterisation</u>

Sixty-four rCDI patients and 64 matched fCDI controls were included (range 8-14 pairs/centre). The pre-planned sample size of 75 matched pairs was not achieved owing to challenges with matching

patients (as described in Figure 1). Patients' demographic and clinical characteristics are summarised in **Table 1**.

Thirty-three percent (21/64) of rCDI patients had severe CDI at the recurrent episode; 52% (33/64) had severe infection at their first episode, compared with 41% (26/64) of the matched fCDI controls. There was considerable heterogeneity in *C. difficile* strains identified, with 27 different ribotypes identified overall. Nine percent (6/64) of rCDIs, 11% (7/64) of the first episodes (in rCDI cases) and 8% (5/64) of fCDIs were attributable to the hypervirulent ribotypes 078 and 027, with other strains (most commonly 002, 014, 015) accounting for the majority of CDI cases. Thirteen rCDI patients (20%) had a different CDI strain compared with the isolate recovered from their first CDI episode (i.e. re-infection).

Six percent (4/64) of rCDI cases (all with mild/moderate CDI) and 14% (9/64) of matched fCDI controls (5 severe, 4 mild/moderate CDI) died within the 28-day post-index period. The median duration of the post-index period in deceased patients was 13-days (IQR=7.3-18.8) for rCDI and 12-days (IQR=9.0-16.0) for fCDI.

Resource utilisation and costs

The total costs of treating rCDI and fCDI patients during the 28-day post-index period are shown in **Table 2**. The median cost per patient was £7,539 (IQR=£5,617-£9,730) for rCDI and £6,294 (IQR=£2,700-£9,216) for fCDI (cost difference, p=0.075). There were some outliers in the fCDI group, with three patients having total costs >£20,000.

Because more fCDI than rCDI patients (9 versus 4, respectively) died during the post-index period, a post-hoc sensitivity analysis was conducted on data from the subgroup of 52 matched pairs where both patients survived to the end of the observation period (i.e. excluding both patients from pairs in which one died). In this group, median costs were similar to those for the overall sample: £7,888 (IQR=£6,047-£9,866) and £6,719 (IQR=£3,329-£9,216) for rCDI and fCDI, respectively (**Table 2**).

The differences in costs between matched rCDI and fCDI patients (cost for rCDI case minus cost for fCDI control) ranged from -£38,163 (fCDI>rCDI) to £11,841 (rCDI>fCDI), with a median difference of £689 (IQR=-£1,873-£3,954) (rCDI>fCDI) (**Figure 2**).

Table 3 shows the breakdown of total costs. The cost of hospital admissions and ED visits accounted for the majority (>85%) of costs for both groups. The median cost for CDI-specific medicines was higher in rCDI patients (£376 per patient [IQR=£31-£1,521]) compared with fCDI (£46 [IQR=£2-£286]) (**Table 3**).

When stratified by severity, the median cost of CDI treatment per patient with severe infection was £5,631 (IQR=£2,910-£9,453) for fCDIs and £8,542 (IQR=£7,463-£10,532) for rCDIs (cost difference, p=0.039). When deceased patients were excluded, median costs were £6,961 (IQR=£4,464-£10,138) and £9,030 (IQR=£7,463-£10,288) for severe fCDIs and rCDIs, respectively (**Table 2**).

The cumulative total number of bed days (median) in rCDI patients during the post-index period was 1,171 (21) days compared with 1,027 (15.5) days for fCDI (difference, p=0.269). The highest median number of bed days (25.5) was observed in patients with a severe rCDI.

The median cost for the between-episode period (rCDI only) was £2,973 (IQR=£778-£4,610) (**Table 2**).

Part 2: Prospective patient self-assessment of QOL

<u>Demographics</u>

Thirty patients completed the EQ-5D-3L questionnaire during a CDI hospitalisation, of whom 63% (19/30) were male. The median age was 70.2 years (IQR=52-77). CDI was severe in 27% of patients (8/30) and mild/moderate in 73% (22/30).

<u>EQ-5D scores</u>

EQ-5D index and VAS scores for patients hospitalised with CDI compared with age-matched population norms are shown in **Figure 3**. The mean EQ-5D index score in CDI patients (0.42 [SD±0.29]) was 46%

lower than the value for patients of similar age (65-74 years) in the UK general population (0.78) (difference, $p<0.001$); similar reduced scores were observed for the VAS (mean 47.82 [SD±21.93] for CDI, 38% lower than the general population score of 77.3, $p<0.001$). EQ-5D dimension scores are shown in **Table 4**.

Discussion

This non-interventional study used a matched retrospective cohort design to estimate the current costs associated with treatment of rCDI in hospitalised patients in the UK. It provides contemporaneous cost-burden data to aid decision-making by payers and clinicians on the targeting of resources for CDI treatment. The study also demonstrates the adverse impact of CDI on HrQoL, which has to-date been a largely neglected area of research. Taken together, the findings highlight the considerable burden that CDI places on patients and healthcare resources and the substantial financial costs associated with both fCDI and rCDI.

In this study, there was considerable heterogeneity of strains causing CDI with 27 different strains identified overall. This pattern is consistent with the epidemiology of CDI in the UK, where no particular ribotypes are dominant and suggests an endemic (non-outbreak) population.[12] It is therefore more representative to the wider UK patient population than data derived during a CDI epidemic.

We found the total cost of treating CDI and hospital LOS to be higher for patients with rCDI compared with fCDI, although these differences were not statistically significant. This may be due to lack of power as a consequence of not meeting the planned sample size, but may also reflect the wide variation in costs between individual patients; this is typical in analyses of healthcare costs and has been observed in previous studies.[1,37] It is also acknowledged that the differences between rCDI and fCDI costs may in part be due to the higher number of deaths in the fCDI group. When deceased patients were excluded, the difference between the groups was smaller than for the whole study sample but the cost remained higher for rCDI than fCDI. Recent systematic reviews have demonstrated incremental costs of $2,871-$4,846/case for primary CDI in US-based[2] studies and £4,577-£8,843 in European studies.[1] Although the median total cost for fCDI in the present study (£6,294) is consistent with these previous estimates, direct comparison is problematic due to methodological differences and variability in costs between different studies, partly due to differences in healthcare systems. Few

studies have estimated the costs associated with rCDI specifically. One US study found that the cost of treating rCDI was $4,948 per-episode,[31,38] which is broadly similar to the £7,539 observed in our study. However, our costs are lower than a recent single centre US study reported by Dubberke *et al.* (attributable costs $11,631 over 180-days)[37] and those reported in a recent abstract (£20,249) presenting the results of a costing analysis in a single UK centre.[39] This may reflect the use of different reference costs or the fact that we used a fixed 28-day observation period. The results of the present study provide an updated estimate of the UK costs associated with treating rCDI, which is important given the lack of contemporaneous data. Recently, new CDI medicines (fidaxomicin and bezlotoxumab) have been developed that have been shown to reduce CDI recurrence rates compared with conventional treatments.[14,15] Our results will help clinical decision makers to evaluate the cost-effectiveness of investing in these new medicines and the potential impact on local service provision. The resource utilisation between CDI episodes in rCDI patients (median £2,973) may represent previously un-recognised costs associated with treatment of patients with CDI once specific CDI treatment has ceased.

Consistent with previous studies, the costs of treating CDI in this study were driven largely by the costs associated with the duration of hospital admissions, which accounted for >85% of total costs in both groups.[40,1] However, the costs of CDI medicines were considerably higher in rCDI patients, reflecting the use of fidaxomicin in recurrent but not fCDI. The median LOS in rCDI cases was 21 days, which is similar to the 20.5 days reported previously in the UK.[40] This similarity is perhaps surprising given that the previous UK study was reported in 1996, and significant efforts have been made to shorten hospital admissions in the intervening period.[41]

The results presented here on the cost of treating CDI according to disease severity are important as PHE recommends different treatment strategies for patients with severe and mild/moderate disease.[42] The highest median total cost was observed in severe rCDI cases (£8,542) and the lowest in patients with severe fCDI (£5,631), although as before, this may be explained partly by the higher number of deaths among fCDI patients with severe disease.

HRQoL in hospitalised CDI patients is dramatically reduced compared with people of similar age in the general population, although from our descriptive study it is unclear whether this is directly attributable to CDI or more generally to the effects of the hospitalisation and associated co-morbidities. Published EQ-5D norms for the general hospital population are not available and comparison with previous studies of hospitalised patients is problematic since most were conducted in patients with specific health conditions or those undergoing surgery, often in single centres or countries outside the UK. In one recent single centre study of patients (of similar age and gender distribution) on adult medical wards in a single UK hospital, the mean EQ VAS at the time of admission was 55.9, 14% higher than the CDI patients in our cohort.[43] This would seem to suggest that the reduced HRQoL is at least partly attributable to CDI, but warrants further research. In our study the usual activities, mobility and self-care EQ-5D dimensions were most affected, which is unsurprising for a group of hospitalised patients. However, the anxiety and depression and pain dimensions were also impaired (63% reported moderate-extreme anxiety/depression; 67% reported moderate-extreme pain). Recent research has demonstrated that anxiety is common in patients hospitalised with CDI, with a number of CDI-specific concerns identified, including worry about future complications, physical concerns about ongoing symptoms and social concerns including interference with daily activities and finances.[16] A limitation of the HRQoL data is that we did not collect information about co-morbidities or whether the patients had a first or recurrent CDI episode; further research is needed to fully understand the impact of each on HRQoL, as well as changes in HRQoL over time.

Strengths and limitations

The primary strength of this study is the matched design for estimation of costs, and the inclusion of descriptive QoL data; the latter is important to enable healthcare providers to determine the overall burden of CDI and has not been widely studied. The study was designed to minimise the impact of bias and confounding factors, however, there are limitations. The quality of the retrospectively-sourced data relies upon the accuracy and completeness of patients' medical records and there were

instances (including medication details) where data were missing or incomplete. This is an inherent limitation of retrospective observational research, however, the impact of missing data in this study should be low because the primary endpoint is driven primarily by LOS, which was well-recorded. Furthermore, cases and controls would be affected equally. Despite age-matching, there were more deaths among fCDI patients, particularly in those with severe CDI; this suggests that either the rCDI patients in this study are a population of patients with less severe disease or that for the healthcare-facility-acquired fCDI cases, the primary reason for hospitalization (not CDI) may be the main determinant of mortality. Although there were some differences in patient characteristics (particularly co-morbidities) between the two cohorts, we did not adjust for these factors in the analysis as they were not considered to be of sufficient magnitude to have introduced major bias into the results. Furthermore, it is not uncommon in CDI cohorts to observe modest imbalances in co-morbidities. We also used clear eligibility criteria and matched patients on the key characteristics related to the disease. The total costs associated with treating CDI may be underestimated because the post-index period was fixed at 28-days; also, the observation period started when CDI was confirmed and patients may have received CDI treatment before this. Only patients with a CDI that was confirmed by testing were included and consequently, the patient population may not be representative of all CDI cases. Testing practices and treatment protocols may have varied between the participating hospitals. These differences were not explored in the analysis owing to the small number of patients per centre and expected variability between individual patients. Despite all available eligible patients being included, the planned sample size of 75 matched pairs was not met due to challenges of matching patients. This may have affected the reliability of the cost estimates and limited the study's ability to identify true differences between the groups. Furthermore, the formal sample size calculation applied only to the overall sample, not to subgroups.

Conclusions

This multicentre study demonstrates that CDI has a considerable impact on both patients and healthcare resources. The data provide an updated estimate of the "real-world" costs associated with rCDI management in the UK. These costs are largely driven by the duration of hospital admissions and are comparable to fCDI costs. The study also indicates increased costs associated with the treatment of patients with severe rCDI; this is important in light of PHE guidance, which recommends different treatment strategies for patients with severe and mild/moderate disease. Overall, the study provides contemporaneous data on the burden of CDI to patients and the healthcare system, which can be used to help clinical decision makers evaluate the cost-effectiveness of new CDI therapeutics, particularly those associated with reduced risk of recurrence.

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Contributorship statement

MHW was involved in the design of the study and the acquisition, analysis and interpretation of the study data. HA was involved in the analysis and interpretation of the study data. JEC and CS were involved in the acquisition and interpretation of the study data. AD, SH and ML were involved in the acquisition, analysis and interpretation of the study data. SMS analysed the data. SWM was involved

in the interpretation of the study data. All authors reviewed the draft manuscript and approved the final version for submission.

Transparency declarations

MHW has received: consulting fees from Actelion, Astellas, bioMerieux, MedImmune, MSD, Pfizer, Qiagen, Sanofi-Pasteur, Seres, Summit, Synthetic Biologics and Valneva; lecture fees from Alere, Astellas, MSD & Pfizer; and grant support from Actelion, Astellas, bioMerieux, Da Volterra, MSD, Sanofi-Pasteur, Seres and Summit.

HA and SWM are employees for the sponsoring company (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA (known as MSD outside the United States and Canada)) that produces a product within the disease area. The funder (and these employees) initiated the study and worked collaboratively with the primary investigator in some of the study design and data analysis. SWM owns stock in Merck & Co., Inc., Kenilworth, NJ USA as part of his compensation.

JEC has participated in an advisory board for MSD (May 2016).

SMS is an employee of pH Associates, an independent research consultancy which was commissioned by the sponsor to provide support with the design and conduct of the study, data analysis and medical writing.

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AD, CS, SH and ML have no conflicts of interest.

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Figure 1: Summary of matched retrospective cohort design and flow of patients through the study

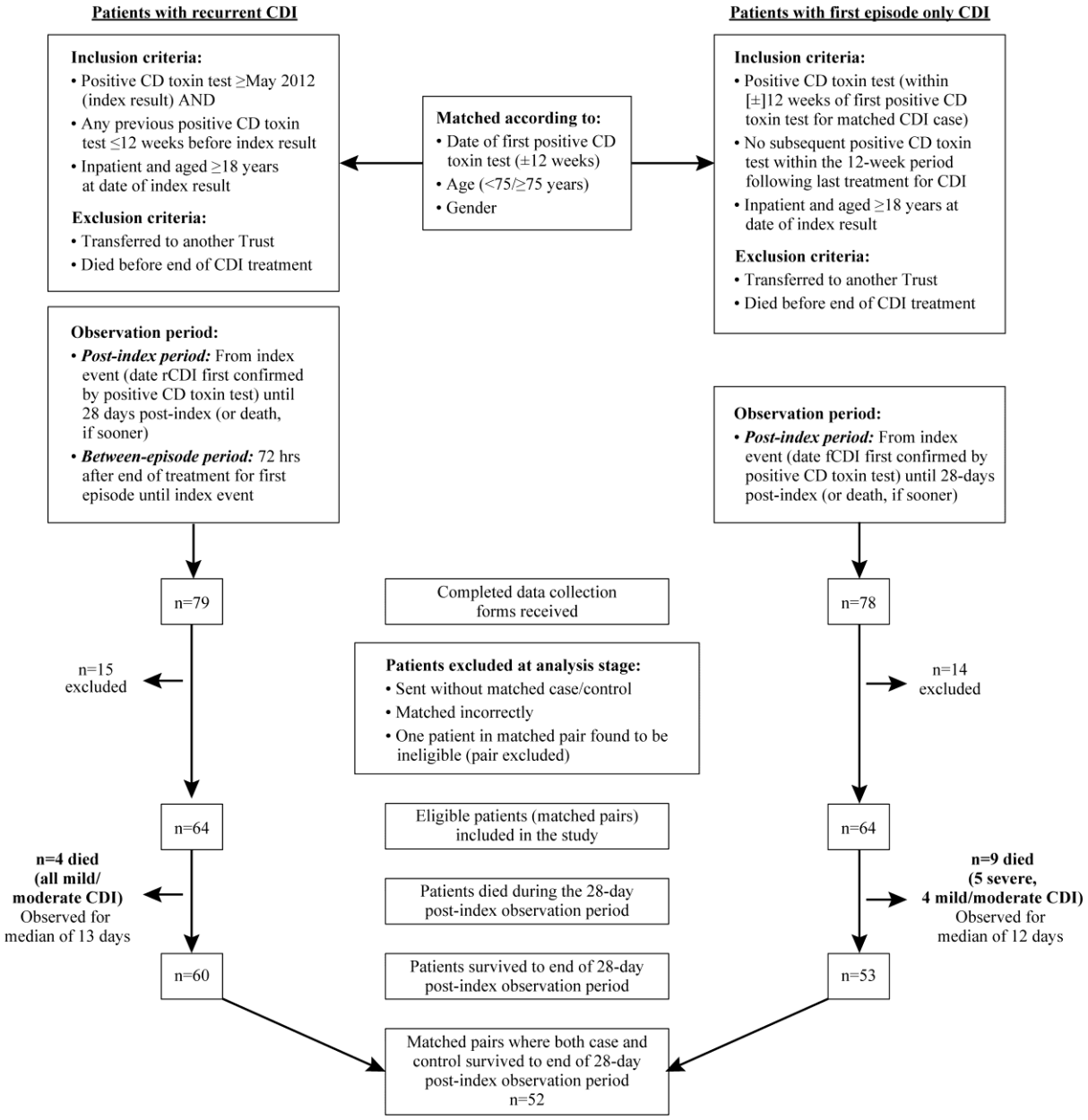


Table 1: Demographic characteristics of patients with rCDI and fCDI

Characteristic	Patients with recurrent CDI		Patients with first episode only CDI
N	64		64
Gender (n, %)			
Male	28 (44%)		28 (44%)
Female	36 (56%)		36 (56%)
Age (years)			
Median	77.0		76.5
Interquartile range	68.5-84.1		66.9-84.1
Co-morbidities (n, %)			
Cardiac disease	18 (28%)		17 (27%)
COPD	19 (30%)		9 (14%)
Hypertension	24 (38%)		19 (30%)
Inflammatory bowel disease	3 (5%)		3 (5%)
Renal disease	5 (8%)		10 (16%)
Alzheimer's/Dementia	9 (14%)		3 (5%)
Atrial fibrillation	6 (9%)		6 (9%)
Osteoarthritis	7 (11%)		6 (9%)
Diabetes	14 (22%)		6 (9%)
Diverticular disease	8 (13%)		9 (14%)
Hypercholesterolemia	1 (2%)		4 (6%)
Hypothyroidism	3 (5%)		2 (3%)
Hyperparathyroidism	1 (2%)		1 (2%)
Cancer	7 (11%)		15 (23%)
Other	56 (88%)		52 (81%)
	First episode	**Recurrent episode**	**First episode**
Setting where CDI acquired			
Community	12 (19%)	4 (6%)	12 (19%)
Healthcare facility	52 (81%)	60 (94%)	52 (81%)
Severity of CDI*			
Mild/moderate	31 (48%)	42 (67%)	38 (59%)
Severe	33 (52%)	21 (33%)	26 (41%)
Strain of CDI			
Hypervirulent ribotypes			
078	6 (9%)	5 (8%)	4 (6%)
027	1 (2%)	1 (2%)	1 (2%)
Other strains (not hypervirulent)	42 (66%)	43 (67%)	44 (69%)
Unassigned/unable to grow	14 (22%)	15 (23%)	10 (16%)
Not done or result unavailable	1 (2%)	0 (0%)	5 (8%)

Abbreviations: CDI, Clostridium difficile infection; COPD, chronic obstructive pulmonary disease

* Unavailable for 1 patient at recurrence; first episode was severe and therefore classified as severe for subsequent analyses

Figure 2: Difference in total costs between individual rCDI cases and matched fCDI controls

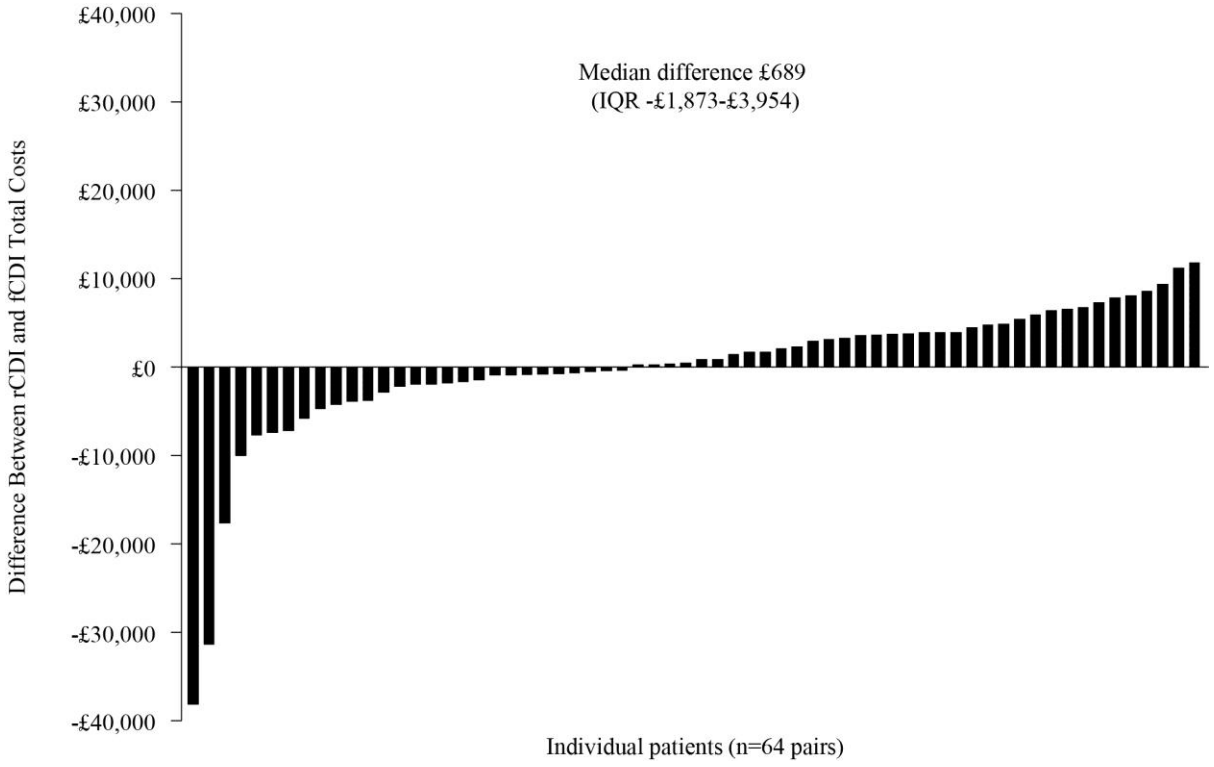


Table 2: Resource utilisation and costs, overall and by CDI severity

	Patients with recurrent CDI			Patients with first episode only CDI		
	Mild/Moderate	**Severe**	**Overall**	**Mild/Moderate**	**Severe**	**Overall**
Total costs (post-index period)*						
All patients	n=42 **£6,675** (£4,419-£8,960)	n=22 **£8,542** (£7,463-£10,352)	n=64 **£7,539** (£5,617-£9,730)	n=38 **£6,518** (£2,652-£9,086)	n=26 **£5,631** (£2,910-£9,453)	n=64 **£6,294** (£2,700-£9,216)
Excluding patients who died (both patients in matched pair excluded if one died)	n=35 **£6,907** (£5,088-£9,290)	n=17 **£9,030** (£7,463-£10,288)	n=52 **£7,888** (£6,047-£9,866)	n=33 **£6,590** (£2,392-£8,906)	n=19 **£6,961** (£4,464-£10,138)	n=52 **£6,719** (£3,329-£9,216)
Total costs (between-episode period)*						
All patients	n=40≠ **£2,683** (£737-£5,351)	n=22 **£3,280** (£1,028-£4,159)	n=62≠ **£2,973** (£778-£4,610)	Not applicable		
Hospital bed days (post-index observation period)*						
All patients	n=42 **15.5** (10-27)	n=22 **25.5** (21-27)	n=64 **21.0** (12-27)	n=38 **20.0** (7-27)	n=26 **14.5** (8-27)	n=64 **15.5** (7-27)
Excluding patients who died (both patients in matched pair excluded if one died)	n=35 **18.0** (12-27)	n=17 **26.0** (22-27)	n=52 **21.0** (13-27)	n=33 **21.0** (6-27)	n=19 **18.0** (11-27)	n=52 **19.5** (7-27)

* Reported as median (IQR) per patient

≠ Two patients excluded (insufficient information to determine inter-episode period)

Table 3: Breakdown of costs associated with treatment of rCDI and fCDI (post-index observation period)

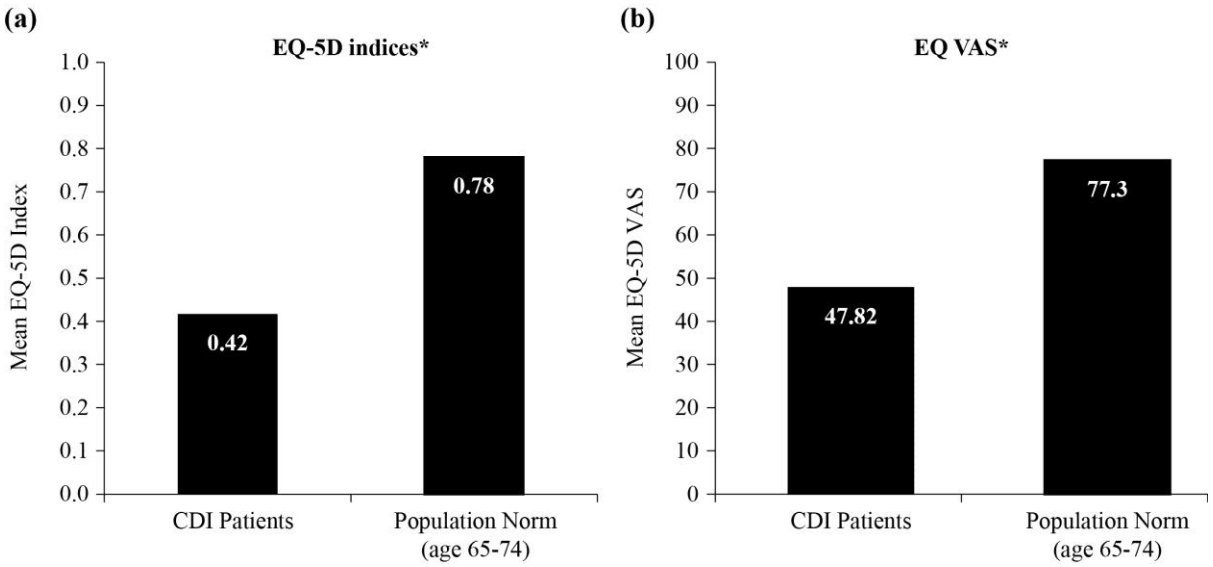
	Patients with recurrent CDI (n=64)*			Patients with first episode only CDI (n=64)*		
Breakdown of costs	**% of total costs**	**Median**	**IQR**	**% of total costs**	**Median**	**IQR**
Hospital bed days	**86.7%**	**£6,033**	£4,002 - £7,767	**88.6%**	**£4,521**	£2,240 - £7,767
CDI-specific medicine[≠]	**5.4%**	**£376**	£31 - £1,521	**0.9%**	**£46**	£2 - £286
Other medicine	**2.4%**	**£170**	£57 - £350	**2.3%**	**£119**	£58 - £299
Lab costs[†]	**4.6%**	**£319**	£190 - £462	**5.9%**	**£304**	£142 - £404
Procedures[†]	**0.8%**	**£54**	£0 - £204	**2.2%**	**£111**	£0 - £277
IV /nutritional support	**0.1%**	**£6**	£0 - £24	**0.1%**	**£4**	£0 - £28
Outpatient visits	**0%**	**£0**	£0-£0	**0%**	**£0**	£0 - £0
Abbreviations: CDI, Clostridium difficile infection; IV, intravenous; IQR, interquartile range						

* Unless otherwise specified

[≠] 23 patients with rCDI were treated with fidaxomicin (median treatment duration 11 days); no patients with fCDI were treated with fidaxomicin

[†] n=54 (one hospital excluded from analysis due to missing data)

Figure 3: EQ-5D of patients hospitalised with CDI compared with UK general population norms for people aged 65-74



* EQ-5D index: maximum score 1 (indicating full health). Lower scores indicate poorer HRQoL; EQ VAS: score range 0-100 (0=Worst imaginable health state, 100=Best imaginable health state)

UK population norms (age 65-74) as published[36]

Table 4: EQ-5D Dimension scores

EQ-5D Dimension		Patients with CDI n=30	
		n	%
Mobility	No problems (1)	11	37%
	Some problems (2)	11	37%
	Confined to bed (3)	8	27%
Self-care	No problems (1)	14	47%
	Some problems (2)	9	30%
	Unable (3)	7	23%
Usual activities	No problems (1)	6	20%
	Some problems (2)	7	23%
	Unable (3)	17	57%
Pain/discomfort	No (1)	10	33%
	Some (2)	16	53%
	Extreme (3)	4	13%
Anxiety/depression	No (1)	11	37%
	Some (2)	15	50%
	Extreme (3)	4	13%